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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/418,095	10/14/1999	JOHN A. COPLAND III	UTMB/GAL:239	8391

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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/23/2003

19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/418,095	COPLAND III ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The finality of the previous Office action is withdrawn. Applicant's first submission after final filed on 2/11/03 has been entered.

Claims 1-46 are pending in the present application.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior Office Action.

Response to Amendment

The rejections of record have been withdrawn, and they have been modified as below.

Upon reconsideration, following is a new ground of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 27 and 39 recite the limitation "the chemotherapeutic agent" in line 1 of the claims. There is insufficient antecedent basis for this limitation in the claim. In claim

1 from which both claims 27 and 39 are dependent upon, "chemotherapeutic drug" is recited not "chemotherapeutic agent".

Claim Rejections - 35 USC § 102

Claims 1-10, 15-16, 27-28, 33-35, 39-42 and 46 are rejected under 35 U.S.C. 102(e) as being anticipated by Urban et al. (U.S. Patent No. 5,814,647 with the effective filing date of 3/4/1997).

Urban et al. teach that troglitazone and related thiazolidinedione compounds (including pioglitazone and BRL49653, see example 1) can be used in the treatment of climacteric symptoms and cancer. Specifically, Urban et al. disclose that therapeutic levels of troglitazone can kill rapidly growing cancerous cells expressing the orphan nuclear receptor PPARγ, while not affecting the viability of normal cells (col. 3, lines 1-9). A type of cancer that is likely to be treated with troglitazone and related thiazolidinedione derivatives are mesenchymal tumors including but not limited to sarcomas, congenital mesoblastic nephroma (**kidney**), rhabdomyosarcomas, fibrosarcomas, retinoblastoma, hemangiopericytoma and mesotheliomas (col. 3, lines 13-22). Urban et al. also stated "Use of troglitazone therapy **in conjunction** with other chemotherapeutic agents, radiation, or surgery may in many cases be the preferred mode of treatment. Troglitazone treatment therefore, would inhibit the growth of the cancer so that other therapies may be added, thereby increasing the likelihood of curing the patient. Troglitazone and related thiazolidinedione derivatives may additionally be used to treat patients with severely metastatic disease. Such treatment may slow tumor

growth and reduce tumor mass, thereby prolonging survival and increasing the quality of terminal cancer patients" (col. 24, lines 17-27). Urban et al. also demonstrated that human breast cancer MCF-7 cells which do not express PPARγ have reduced cell viability at high concentrations of troglitazone (see example 6 and Fig. 13). Urban et al. further teach for preparing pharmaceutical compositions, pharmaceutically acceptable carriers can be either solid (e.g., powders, tablets, pills, suppositories) or liquid (e.g., solutions, suspensions, emulsions); and that oral administration and/or parenteral injection of the compositions can be used (see col. 19-20). The quantity of active components in a unit dose preparation may be varied or adjusted from 0.1 mg to 100 mg, preferably 0.5 mg to 100 mg according to particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents (col. 20, lines 8-18).

The teachings of Urban et al. meet every limitation of the instant claims, and therefore the reference anticipates the presently claimed invention.

Claim Rejections - 35 USC § 103

Claims 1, 16-25, 28-29 and 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Urban et al. (U.S. Patent No. 5,814,647 with the effective filing date of 3/4/1997) in view of Medenica et al. (U.S. Patent No. 5,736,129).

Urban et al. teach that troglitazone and related thiazolidinedione compounds (including pioglitazone and BRL49653, see example 1) can be used in the treatment of climacteric symptoms and cancer. Specifically, Urban et al. disclose that therapeutic

levels of troglitazone can kill rapidly growing cancerous cells expressing the orphan nuclear receptor PPARγ, while not affecting the viability of normal cells (col. 3, lines 1-9). A type of cancer that is likely to be treated with troglitazone and related thiazolidinedione derivatives are mesenchymal tumors including but not limited to sarcomas, congenital mesoblastic nephroma (**kidney**), rhabdomyosarcomas, fibrosarcomas, retinoblastoma, hemangiopericytoma and mesotheliomas (col. 3, lines 13-22). Urban et al. also stated "Use of troglitazone therapy **in conjunction** with other chemotherapeutic agents, radiation, or surgery may in many cases be the preferred mode of treatment. Troglitazone treatment therefore, would inhibit the growth of the cancer so that other therapies may be added, thereby increasing the likelihood of curing the patient. Troglitazone and related thiazolidinedione derivatives may additionally be used to treat patients with severely metastatic disease. Such treatment may slow tumor growth and reduce tumor mass, thereby prolonging survival and increasing the quality of terminal cancer patients" (col. 24, lines 17-27). Urban et al. also demonstrated that human breast cancer MCF-7 cells which do not express PPARγ have reduced cell viability at high concentrations of troglitazone (see example 6 and Fig. 13). Urban et al. further teach for preparing pharmaceutical compositions, pharmaceutically acceptable carriers can be either solid (e.g., powders, tablets, pills, suppositories) or liquid (e.g., solutions, suspensions, emulsions); and that oral administration and/or parenteral injection of the compositions can be used (see col. 19-20). The quantity of active components in a unit dose preparation may be varied or adjusted from 0.1 mg to 100 mg, preferably 0.5 mg to 100 mg according to particular application and the potency of

the active component. The composition can, if desired, also contain other compatible therapeutic agents (col. 20, lines 8-18).

Urban et al. do not teach explicitly the types of chemotherapeutic drugs utilized in combination with the troglitazone therapy or the recited route of administration (e.g., regionally, intravenously, percutaneoulsy, perfusion) or resecting any tumor.

However at the effective filing date of the present application, different types of chemotherapeutic drugs, different routes of administering drugs as well as resecting tumors have been utilized in cancer treatment. Medenica et al. teach the use a multidrug chemotherapeutic regimen for cancer treatment in a patient. The utilized drugs that are taught in the issued patent encompass alkylating agents such as Cis-platin, cyclophosphamide; mitotic inhibitors such as etoposide or VP-16, taxol, vinblastine; antibiotics such as doxorubicin, dactinomycin; an antimetabolite such as 5-FU, a corticosteroid hormone such as prednisone as well as chlorethel-methyl-cycloexyl-nitrosourea (See col. 6-10; and col. 22, lines 18-19). Medenica et al. specifically teach that it is known that a chemotherapeutic treatment regimen utilizing several drugs may be more effective than the best single drug, particularly a degree of potentiation exists between the agents in their efficacy against tumor cells to a greater extent than normal cells (col. 2; lines 42-55), and that the multidrug regimen has low toxicity insofar as ineffective chemotherapeutic agents are eliminated from the regimen (col. 5, lines 35-38). Medenica et al. also teach the removal of a cancer specimen taken from a human cancer patient for determining drug samples having the highest cancer cell pharmacosensitivity (line 53 of col. 4 continues to line13 of col. 5), and that bladder

cancer, breast cancer, colon carcinoma, non-small cell lung cancer, pancreatic cancer, liver cancer, prostatic carcinoma, acute myeloid leukemia, glioblastoma, osteogenic sarcaoma, ovarian carcinoma and others have all responded to the multidrug treatment (col. 11, lines 13-23). Medenica et al. also teach that the multidrug regimen may be administered by any of the methods known in the art, such as intravenous administration or even oral administration, particularly locoregional administration (locoregional intra-arterial infusion) or perfusion of chemotherapy to enhance the delivery of drug to the tumor due to its small blood supply (see the section titled "Administration of the Regimen", particularly col. 27, first full paragraph).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to modify the method taught by Urban et al. by using the specific recited chemotherapeutic drugs taught by Medenica et al. **in conjunction** with a thiazolidinedione compound (e.g., troglitazone, pioglitazone and rosiglitazone) to inhibit the growth or killing tumor cells; particularly via locoregional intra-arterial infusion or perfusion administration of the pharmaceutical composition for treating a cancer patient.

One of ordinary skilled artisan would have been motivated to carry out the above modification because as taught by Urban et al. the utilization of chemotherapeutic agents such as those taught by Medenica et al. **in conjunction** with the use of troglitazone or a thiazolidinedione compound increases the likelihood of curing a cancer patient. Additionally, Medenica et al. specifically teach that it is known that a chemotherapeutic treatment regimen utilizing several drugs may be more effective than

the best single drug, particularly a degree of potentiation exists between the agents in their efficacy against tumor cells to a greater extent than normal cells (col. 2; lines 42-55), and that the multidrug regimen has low toxicity insofar as ineffective chemotherapeutic agents are eliminated from the regimen (col. 5, lines 35-38). Furthermore, one of ordinary skilled artisan would have been motivated to administer the pharmaceutical composition into a cancer patient via locoregional intra-arterial infusion or perfusion to enhance the delivery of drug(s) to the tumor due to its small blood supply as taught by Medenica et al. (see the section titled "Administration of the Regimen", particularly col. 27, first full paragraph). One of ordinary skilled artisan would also have been motivated to resect the tumor to decrease tumor burden in the patient or for obtaining a tumor specimen for determining chemotherapeutic drug samples having the highest cancer cell pharmacosensitivity as taught by Medenica et al. (line 53 of col. 4 continues to line13 of col. 5).

One of ordinary skilled artisan would have a reasonable expectation of success because Urban et al. clearly teach that therapeutic levels of troglitazone or thiazonlidinedione compound can kill rapidly growing cancerous cells expressing the orphan nuclear receptor PPARγ, while not affecting the viability of normal cells (col. 3, lines 1-9); and that even with human breast cancer MCF-7 cells which do not express PPARγ have reduced cell viability at high concentrations of troglitazone (see example 6 and Fig. 13). Additionally, bladder cancer, breast cancer, colon carcinoma, non-small cell lung cancer, pancreatic cancer, liver cancer, prostatic carcinoma, acute myeloid leukemia, glioblastoma, osteogenic sarcaoma, ovarian carcinoma and others have all

responded to the multidrug chemotherapeutic treatment taught by Medenica et al. (col. 11, lines 13-23).

Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1, 25 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Urban et al. (U.S. Patent No. 5,814,647 with the effective filing date of 3/4/1997) in view of Medenica et al. (U.S. Patent No. 5,736,129) as applied to claims 1, 16-25, 28-29 and 36-38 above, and further in view of Jin et al. (U.S. Patent No. 6,251,871 with the effective filing date of 7/17/1995).

The combined teachings of Urban et al. and Medenica et al. have been discussed and applied above. However, none of the references teaches explicitly a step of further contacting the cancer cell with a therapeutic polynucleotide as recited in claim 32.

However, at the effective filing date of the present application Jin et al. already teach a method for inhibiting tumor growth (e.g., lung cancer tumor, bladder cancer tumor, a glioma, a melanoma, a head and neck cancer tumor) in a mammal by direct intratumoral administration of a recombinant vector encoding a p16 gene product (see abstract and claims). Additionally, Jin et al. teach that the p16 replacement therapy could be used **in conjunction** with chemo or radiotherapeutic intervention to improve the efficacy of chemo- and radiotherapy (see col. 19, lines 46-56; and section E on cols. 19-22). Moreover, Jin et al. teach gene therapies involving polynucleotides of p21, Rb,

APC, DCC, NF-1, NF-2, WT-1, MEN-I, MEN-II, BRCA1, VHL, FCC, MCC, ras, myc, neu, raf, erb, src, fms, jun, trk, ret, gsp, hst, bcl and abl can also be used (line 66 of col. 21 continues to line 7 of col. 22).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to further modify the combined method taught by Urban et al. and Medenica et al. by further contacting the cancer cell with a polynucleotide of p16 or other therapeutic polynucleotides taught by Jin et al. for further inhibiting the growth or further killing tumor cells.

One of ordinary skilled artisan would have been motivated to further carry out the above modification to increase the efficacy of tumor cell killing or cancer growth inhibition as clearly taught by Jin et al.

Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1, 28 and 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Urban et al. (U.S. Patent No. 5,814,647 with the effective filing date of 3/4/1997) in view of Roth et al. (U.S. Patent No. 5,747,469).

Urban et al. teach that troglitazone and related thiazolidinedione compounds (including pioglitazone and BRL49653, see example 1) can be used in the treatment of climacteric symptoms and cancer. Specifically, Urban et al. disclose that therapeutic levels of troglitazone can kill rapidly growing cancerous cells expressing the orphan nuclear receptor PPARγ, while not affecting the viability of normal cells (col. 3, lines 1-

9). A type of cancer that is likely to be treated with troglitazone and related thiazolidinedione derivatives are mesenchymal tumors including but not limited to sarcomas, congenital mesoblastic nephroma (**kidney**), rhabdomyosarcomas, fibrosarcomas, retinoblastoma, hemangiopericytoma and mesotheliomas (col. 3, lines 13-22). Urban et al. also stated radiation, or surgery may in many cases be the preferred mode of treatment. Troglitazone treatment therefore, would inhibit the growth of the cancer so that other therapies may be added, thereby increasing the likelihood of curing the patient. Troglitazone and related thiazolidinedione derivatives may additionally be used to treat patients with severely metastatic disease. Such treatment may slow tumor growth and reduce tumor mass, thereby prolonging survival and increasing the quality of terminal cancer patients" (col. 24, lines 17-27). Urban et al. also demonstrated that human breast cancer MCF-7 cells which do not express PPARγ have reduced cell viability at high concentrations of troglitazone (see example 6 and Fig. 13). Urban et al. further teach for preparing pharmaceutical compositions, pharmaceutically acceptable carriers can be either solid (e.g., powders, tablets, pills, suppositories) or liquid (e.g., solutions, suspensions, emulsions); and that oral administration and/or parenteral injection of the compositions can be used (see col. 19-20). The quantity of active components in a unit dose preparation may be varied or adjusted from 0.1 mg to 100 mg, preferably 0.5 mg to 100 mg according to particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents (col. 20, lines 8-18).

Urban et al. do not teach explicitly the type of radiation utilized in combination with the troglitazone therapy for inhibiting the growth of a cancer cell.

However, at the effective filing date of the present application Roth et al. already disclose a method of killing cancerous cells using a tumor suppressor gene, p53 in a recombinant retrovirus, in combination with a DNA damaging agent. An embodiment of the invention disclosed by Roth et al. involves the use of gamma-irradiation, X-rays, UV-irradiation or microwaves as a DNA damaging agent (DNA damaging agent also encompasses chemotherapeutic agents such as 5FU, etoposide, camptothecin, mitomycin C, cisplastin) in combination with p53 gene transfer to treat cancer (column 8, second paragraph and see claims 51 and 61-67). Roth et al. further noted that a combination treatment is required to prevent local recurrence following primary tumor resection (See column 3, lines 20-25).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to modify the method taught by Urban et al. by using the specific recited irradiation taught by Roth et al. **in conjunction** with a thiazolidinedione compound (e.g., troglitazone, pioglitazone and rosiglitazone) to inhibit the growth or killing tumor cells.

One of ordinary skilled artisan would have been motivated to carry out the above modification to increase the efficacy of tumor cell killing or cancer growth inhibition. Urban et al. clearly teach that the use of troglitazone therapy **in conjunction** with other chemotherapeutic agents, radiation, or surgery may in many cases be the preferred mode of treatment because of the increased likelihood of curing the patient.

One of ordinary skilled artisan would have a reasonable expectation of success because Urban et al. clearly teach that therapeutic levels of troglitazone or thiazonlidinedione compound can kill rapidly growing cancerous cells expressing the orphan nuclear receptor PPARγ, while not affecting the viability of normal cells (col. 3, lines 1-9); and that even with human breast cancer MCF-7 cells which do not express PPARγ have reduced cell viability at high concentrations of troglitazone (see example 6 and Fig. 13). Additionally, Roth et al. have already shown successfully the use of gamma-irradiation, X-rays, UV-irradiation or microwaves as a DNA damaging agent (DNA damaging agent also encompasses chemotherapeutic agents such as 5FU, etoposide, camptothecin, mitomycin C, cisplastin) in combination with p53 gene transfer for treating cancer.

Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1, 9, 11-14, 40 and 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Urban et al. (U.S. Patent No. 5,814,647 with the effective filing date of 3/4/1997) in view of Pitot (In Fundamentals of Oncology, 3rd Edition, pages 29-32, 1986).

Urban et al. teach that troglitazone and related thiazolidinedione compounds (including pioglitazone and BRL49653, see example 1) can be used in the treatment of climacteric symptoms and cancer. Specifically, Urban et al. disclose that therapeutic levels of troglitazone can kill rapidly growing cancerous cells expressing the orphan

nuclear receptor PPARγ, while not affecting the viability of normal cells (col. 3, lines 1-9). Urban et al. teach "Studies show that troglitazone is a ligand for the orphan nuclear receptor PPARγ. Translocation of this transcription factor in the nucleus of cells at sufficient rates inhibits transcription and reduces progesterone production in normal granulosa cells without a loss of viability. However, this inhibition of transcription in rapidly dividing cancer cells expressing receptor PPARγ results in the loss of cell viability and inhibition of cell growth." (col. 3, lines 23-30). A type of cancer that is likely to be treated with troglitazone and related thiazolidinedione derivatives are mesenchymal tumors including but not limited to sarcomas, congenital mesoblastic nephroma (**kidney**), rhabdomyosarcomas, fibrosarcomas, retinoblastoma, hemangiopericytoma and mesotheliomas (col. 3, lines 13-22). Urban et al. also stated "Use of troglitazone therapy **in conjunction** with other chemotherapeutic agents, radiation, or surgery may in many cases be the preferred mode of treatment. Troglitazone treatment therefore, would inhibit the growth of the cancer so that other therapies may be added, thereby increasing the likelihood of curing the patient. Troglitazone and related thiazolidinedione derivatives may additionally be used to treat patients with severely metastatic disease. Such treatment may slow tumor growth and reduce tumor mass, thereby prolonging survival and increasing the quality of terminal cancer patients" (col. 24, lines 17-27). Urban et al. also demonstrated that human breast cancer MCF-7 cells which do not express PPARγ have reduced cell viability at high concentrations of troglitazone (see example 6 and Fig. 13). Urban et al. further teach for preparing pharmaceutical compositions, pharmaceutically acceptable carriers

can be either solid (e.g., powders, tablets, pills, suppositories) or liquid (e.g., solutions, suspensions, emulsions); and that oral administration and/or parenteral injection of the compositions can be used (see col. 19-20). The quantity of active components in a unit dose preparation may be varied or adjusted from 0.1 mg to 100 mg, preferably 0.5 mg to 100 mg according to particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents (col. 20, lines 8-18).

Urban et al. do not teach explicitly the cancer cell is a bone cancer cell, osteosarcoma cell, precursor of osteosarcoma cell, or ovarian cancer cell.

However, at the effective filing date of the present application, Pitot teaches that osteoma (benign bone cancer or precursor of osteosarcoma) and osteogenic sarcoma (malignant form or osteosarcoma) are derived from the mesodermal (mesenchymal) embryonic germ layer, and therefore they belongs to mesenchymal tumors (page 31, bottom of the first full paragraph and Table 2.1). Additionally, Pitot teaches that granulose cell tumor is a benign cancer of the ovary (see bottom of Table 2.1).

Accordingly, it would have been obvious for an ordinary skilled artisan to utilize troglitazone or thiazolidinedione compound in conjunction with other chemotherapeutic agents, radiation, or surgery to inhibit the growth of the recited cancer cells because bone cancer cells, precursors of osteosarcoma and osteosarcoma are classified as mesenchymal tumors as taught by Pitot. Furthermore, granulosa cell tumor is a benign neoplasm of ovary, whose growth and cell viability are inhibited by the action of troglitazone that has no effect on normal granulosa cells.

One of ordinary skilled artisan would have been motivated to carry out the above modification because Urban et al. clearly teach that troglitazone and related thiazolidinedione derivatives are useful for treating a broad range of mesenchymal tumors including but not limited to sarcomas, congenital mesoblastic nephroma (**kidney**), rhabdomyosarcomas, fibrosarcomas, retinoblastoma, hemangiopericytoma and mesotheliomas (col. 3, lines 13-22).

One of ordinary skilled artisan would also have a reasonable expectation of success because even with human breast cancer MCF-7 cells which do not express PPARγ decreased tumor cell viability at high concentrations of troglitazone was still obtained (see example 6 and Fig. 13).

Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejections in the Appeal Brief filed on 2/11/03 in Paper No. 17 have been fully considered.

Applicants argue basically that prior to the Applicants' disclosure it was not known whether the use of thiazolidinedione therapy in combination with other chemotherapeutic agents or radiation would inhibit the growth of a cancer cell, and that the disclosure of Urban on the use of troglitzone in combination with chemotherapeutic drugs or radiation was not based on actual experiments. Applicants further argue that due to the lack of predictability in the art, the disclosure of Urban would not enable one

of ordinary skill in the art to make and use the presently claimed invention. Applicants' arguments are respectfully found unpersuasive for the following reasons.

Firstly, Urban clearly teach the essential concept of using troglitazone (as well as related thiazolidinedione compounds such as pioglitazone and BRL49653) therapy **in conjunction** with other chemotherapeutic agents, radiation, or surgery for the treatment of cancer. According to Webster's Dictionary, the term "conjunction" means union or concurrence (taking place at the same time or accompanying) of events. Therefore, Urban et al. anticipate the instant claimed invention.

Secondly, with respect to Applicants' argument on the unpredictability of the art, it is unclear which unpredictable factors are involved in cancer treatment or killing cancer cells via the combined uses of troglitazone or related thiazolidinedione compounds with other chemotherapeutic agents, radiation or surgery. Chemotherapeutic agents, radiation or surgery were routinely used in cancer treatment at the effective filing date of the present application as evidenced by the teachings of Medenica et al., Jin et al. and Roth et al., for examples. In addition to the teachings of Urban et al. on the use of troglitazone and related thiazolidinedione compounds to kill transformed cell lines and even with human breast cancer MCF-7 cells that do not express PPARγ (see examples 5 & 6), at the effective filing date of the present application Mueller et al. (Mol. Cell 1:465-470, 1998; Cited previously) demonstrated that troglitazone or pioglitazone decreases the growth of human breast cancer 21PT cells; Brockman et al. (Gastroenterology 115:1049-1055, 1998; Cited previously) showed that BRL 49653 or rosiglitazone inhibits the growth of human colon cancer cells

derived from various cell lines HCA-7, HCT-116, HCT-15 and HCT-15-G25; Elstner et al. (Proc. Natl. Acad. Sci. USA 95:8806-8811, 1998; Cited previously) disclosed clonal proliferation of human breast cancer cells derived from cell lines MCF7, T47D, MDA-MB-231 were inhibited by troglitazone (TGZ) in a concentration-dependent manner, and that this inhibition was further enhanced with the combination of TGZ and all-*trans*-retinoic acid (ATRA) which is an anti-neoplastic chemotherapeutic agent; Kubota et al. (Cancer Res. 58:3344-3352, 1998; Cited previously) taught that troglitazone and other PPAR-gamma ligands including BRL49653 and others have anti-proliferative effects on the human PC-3 prostate cancer cells; and Tontonoz et al. (Proc. Natl. Acad. Sci. 94:237-241, 1997; IDS) disclosed that thiazolidinedione compounds such as pioglitazone, troglitazone and BRL49653 (rosiglitazone) can induce terminal differentiation of human liposarcoma cells *in vitro*, and that thiazolidinedione-induced differentiation of liposarcoma cells is accompanied by cell cycle growth arrest, which is in effect inhibiting liposarcoma cell growth.

Thirdly, Examiner also would like to direct Applicants to the claims of U.S. Patent No. 6,207,690 issued to Urban et al., which are directed to methods of treating a tumor in a subject using troglitazone, pioglitazone and BRL 49653. This patent claims priority to the cited U.S. Patent No. 5,814,647, and it contains the same example relating to the effects of troglitazone on the viability of human MCF-7 cancer cells, indicating that the disclosure of U.S. Patent No. 5,814,647 is enabled for the use of a thiazolidinedione compound for treating cancer. Do Applicants question the validity of the claims of issued U.S. Patent No. 6,207,690?

Fourthly, Examiner noted that Applicants solely disclosed the growth inhibitory effects of troglitazone, pioglitazone or BRL49653 alone or in combination with chemotherapeutic agents on cultured osteosarcoma cells, cultured human renal tumor cells and cultured human ovarian cancer cells. With the respect to Applicants' argument on the unpredictability of the art, do Applicants also question the enablement of their own claims directed to *in vivo* methods, particularly for those that recite therapeutic effects?

Therefore, it is unclear what exactly is not predictable regarding to the combined uses of troglitazone or related thiazolidinedione compounds with other chemotherapeutic agents, radiation or surgery for treating or killing cancer cells? Applicants have failed to provide any factual evidence or reasonable scientific reasoning what or why the art is unpredictable from the combined uses of troglitazone or related thiazolidinedione compounds with other chemotherapeutic agents, radiation or surgery for treating or killing cancer cells, particularly when taken the state of the relevant art as a whole at the effective filing date of the present application as discussed above.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (703) 308-1906, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER